

LETTER TO EDITOR

Evolution of anti-IgE treatment

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The central role played by IgE antibodies in the pathophysiology of allergic diseases makes anti-IgE treatment of paramount importance. However, the development of anti-IgE drugs has taken more than two decades, from the first *in vitro* experiments in the 1970s to the availability of omalizumab as a safe and effective agent.¹ Omalizumab was evaluated in a large number of studies following its approval by regulatory agencies for the treatment of severe allergic asthma not controlled by standard drug therapy. Based on a Cochrane meta-analysis of 25 trials on adults and children, omalizumab was shown to be well-tolerated and effective in reducing asthma exacerbation and hospitalization when used as an adjunctive therapy to inhaled steroids and during steroid tapering phases. For future studies of omalizumab, the authors suggest carrying out a further assessment of pediatric populations, a direct double-dummy comparison with inhaled corticosteroids, a determination of the performance of prospective studies on the prednisolone-sparing effect and, given the high cost of the drug, the identification of biomarkers that are predictive of response.² However, a systematic review of all trials reporting economic data showed a clear cost-effectiveness, as assessed by parameters such as incremental cost-effectiveness ratio and quality-adjusted life-year, primarily due

to the reduction of asthma exacerbations, with incremental cost-effectiveness above conventional national health system thresholds of cost-effectiveness.³ Indeed, anti-IgE treatment may be improved by developing new agents, as is the case for any field of medical treatment. In the present issue of this journal, Nyborg and coworkers describe a new anti-IgE antibody (MEDI4212) that, instead of blocking the interaction between IgE and the Fcε receptor on effector cells, as done by omalizumab, is aimed at neutralizing soluble IgE and eliminate IgE-expressing B lymphocytes through antibody dependent cell-mediated cytotoxicity.⁴ The main rationale for developing this agent was to increase the antibody affinity for its receptors by generating variants containing mutations in the Fc region or alterations in fucosylation. For each MEDI4212 variant, the affinity with human IgE was comparable to the wild-type antibody, and each of them inhibited the interaction of IgE with FcεRI, resulting in strong inhibition of FcεRI-mediated responses. All variants bound similarly to IgE at the membrane surface of IgE expressing cells, but demonstrated enhanced affinity for FcεRIIIa, leading to increased effector function in cell-based (including cell lines and class-switched human IgE B cells) assays. Based on these characteristics, the authors suggest that the major advantages of MEDI4212 over omalizumab are the ability to neutralize high levels of soluble IgE and to eliminate IgE-expressing B cells before they differentiate and become IgE-secreting plasma cells. The latter effect could be of crucial importance in providing a long-term clinical benefit

based on a lasting immunological modification. Indeed, studies on the persistence of omalizumab efficacy after stopping treatment are available. Nopp *et al.*⁵ reported that a group of patients with severe allergic asthma treated for 6 years with omalizumab had mild and stable asthma, accompanied by a considerable downregulation of basophil allergen sensitivity, 3 years after treatment withdrawal. In contrast, Molimard *et al.*⁶ observed a loss of asthma control in 55.7% of patients from a population of 61 individuals who had discontinued omalizumab because of clinical success after a mean duration of 22.7 ± 13.1 months of treatment. One may argue that treatment duration is crucial. In the study by Molimard, no correlation was detected between time to loss of asthma control and duration of treatment, but it should be noted that no patient was treated for more than three years. However, in Nopp's study, all patients were treated for six years. Only specific follow-up studies will be able to clarify the supposed superiority of MEDI4212 in providing a longer duration of clinical control of asthma compared to omalizumab after discontinuation. Furthermore, specific studies are needed to determine if the new anti-IgE antibody is effective on pathologies other than allergic asthma, especially non-IgE-mediated diseases, which is a feature of omalizumab.⁷ In particular, the efficacy of omalizumab on chronic idiopathic or spontaneous urticaria, which was demonstrated in a large group of 323 patients who did not respond to antihistamine therapy at approved doses,⁸ had led to its licensing in the United States and Europe for

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spontaneous, drug resistant urticaria. In this study, the patients had no demonstrated allergic causes of urticaria, but had a mean IgE level of 168.2 ± 231.9 kU/l. Chang *et al.*⁹ argued that IgE, by binding to FcεRI on mast cells, can promote their proliferation and survival, decrease the release threshold and increase their sensitivity to various stimuli through either FcεRI or other receptors for the degranulation process. Thus, omalizumab treatment, by blocking the interaction between IgE and its receptor, can likely attenuate the multiple effects of IgE to maintain and enhance mast cell activities and, hence, reduce the ability of mast cells to elicit inflammatory mechanisms in patients with urticaria.

A deeper understanding of the mechanisms of omalizumab action as well as novel anti-IgE antibodies will

further improve the effectiveness of anti-IgE treatment towards its multifaceted targets, and particularly to its major goal of controlling severe asthma unresponsive to common drug treatment.

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